Mathematical Modeling of Vascular Endothelial Cell Responsiveness to Flow

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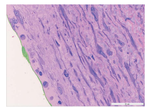
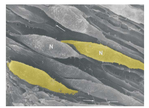
Introduction



Endothelium: Monolayer of cells that lines interior of arteries



Endothelial cells (EC) regulate normal vascular function
- **Modulate vascular tone in response to acute changes in blood flow**
- **Remodel vascular wall structure in response to chronic hemodynamic changes**

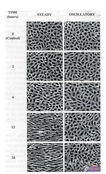
Figures from UIUC College of Medicine Internet Atlas of Histology.URL: http://www.med.uiuc.edu/histo/large/atlas/index.htm

Motivation

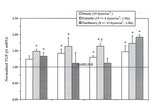
Numerous studies have shown that ECs exhibit different responses to constant and oscillatory shear stresses.

Clinical studies
- **Early atherosclerotic lesions localize preferentially in regions of low and/or oscillatory shear stress.**
- **Regions subjected to high and unidirectional shear stress largely remain spared.**

Shear stress elicits biological responses from EC



Induce extensive changes in cytoskeleton

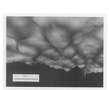


Alter expression of important genes

Figures from LWB00

Crucial discovery (WBI93)

Applied mechanical stresses to cell surface receptors (integrins)



Induced focal adhesion formation (from DRG94)

Supported force-dependent stiffening response of cytoskeleton

Results suggest that
- **Integrins act as mechanoreceptors**
- **Integrins transmit forces to cytoskeleton**
- **Cytoskeleton rearranges to mediate signal transduction**

EC Sensory Scheme

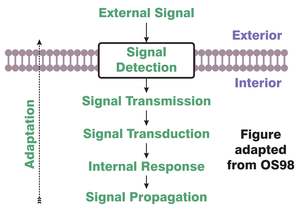
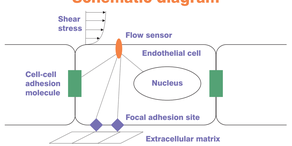


Figure adapted from OS98

Schematic diagram



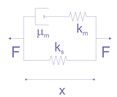
This work

Mechanical model addresses
- **Signal detection**
- **Signal transmission**

Mechanosensitive molecule addresses
- **Signal transduction**

Mechanical Model Development

Assume protein is linear viscoelastic solid. Formulate as three-parameter Maxwell model (Tsc89):



$$\tau_\epsilon = \mu_m/k_m \qquad \tau = \mu_m/k_s \qquad \tau_\sigma = \tau_\epsilon + \tau$$

Governing equation & initial condition:

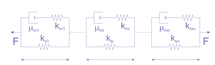
$$k_s\,\tau_\sigma\frac{dx}{dt} + k_s\,x = F + \tau_\epsilon\frac{dF}{dt} \qquad x(0) = \frac{F_0}{(k_s + k_m)}$$

External Signals

$$\text{Steady forcing: } F = F_0$$

$$\text{Oscillatory forcing: } F = F_0\cos(\omega t)$$

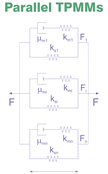
Series TPMMs



There are n constraints on force

$$F_1 = F \cdots F_i = F \cdots F_n = F$$

Parallel TPMMs

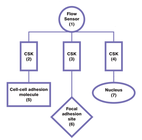


There are (n-1) constraints on length and 1 constraint on force

$$\begin{aligned} x_1 &= x_2 \\ &\vdots \\ x_{i-1} &= x_i \\ &\vdots \\ x_{n-1} &= x_n \\ \sum_{j=1}^{n} F_j &= F \end{aligned}$$

Complex networks are composed of combinations of series and parallel configurations.

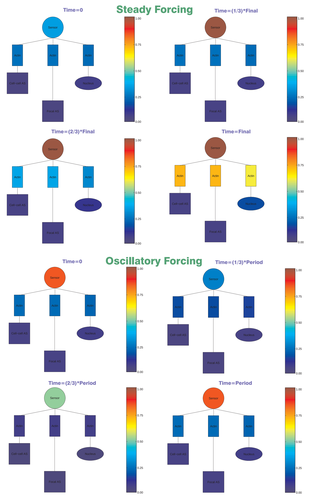
Graph representation



$$\begin{aligned} (k_s\,\tau_\sigma)_j\frac{dx_j}{dt} - (\tau_\epsilon)_j\frac{dF_j}{dt} &= -(k_s)_j\,x_j + F_j \\ 0 &= x_j - x_{j+1} \\ 0 &= \sum_{j=1}^{n} F_j - F(t) \\ 0 &= F_j - F(t) \\ j &\in \{1,\ldots,n\} \end{aligned}$$

$$\begin{aligned} \mathrm{M}\frac{d\mathrm{y}}{dt} &= \mathrm{Sy} + \mathrm{Bu} \\ \mathrm{y} &:= [x_1,\ldots,x_n,F_1,\ldots,F_n]^T \\ \mathrm{M} &= \begin{bmatrix} \mathrm{M}_{11} & \mathrm{M}_{12} \\ 0 & 0 \end{bmatrix} \\ \mathrm{S} &= \begin{bmatrix} \mathrm{S}_{11} & \mathrm{S}_{12} \\ \mathrm{S}_{21} & \mathrm{S}_{22} \end{bmatrix} \\ \mathrm{B} &= \begin{bmatrix} \mathrm{B}_1 & \mathrm{B}_2 \end{bmatrix}^T \\ \mathrm{u} &= [F(t)] \\ \mathrm{M}_{11} &= \mathrm{diag}\left[(k_s\,\tau_\sigma)_j\right],\ j\in\{1,\ldots,n\} \\ \mathrm{M}_{12} &= \mathrm{diag}\left[-(\tau_\epsilon)_j\right],\ j\in\{1,\ldots,n\} \\ \mathrm{S}_{11} &= \mathrm{diag}\left[-(k_s)_j\right],\ j\in\{1,\ldots,n\} \\ \mathrm{S}_{12} &= \mathrm{I} \\ \mathrm{S}_{21} &= \mathrm{sparse}\left[\{0,1,-1\}\right] \\ \mathrm{S}_{22} &= \mathrm{sparse}\left[\{0,1,-1\}\right] \\ \mathrm{B}_1 &= \begin{bmatrix} 0 & \cdots & 0 \end{bmatrix}^T \\ \mathrm{B}_2 &= \begin{bmatrix} 0 & \cdots & 0 & -1 & 0 & \cdots & 0 \end{bmatrix}^T \end{aligned}$$

Mechanical model for EC shear stress detection and transduction (MTB03)

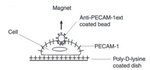


All deformations are normalized to the range 0–1. The low end corresponds to zero deformation and the high end corresponds to the largest deformation encountered under constant forcing. Each forcing is depicted over a relevant time scale. The oscillatory case shows that the flow sensor deforms almost as much as in the steady case. The actin filaments under the oscillatory case experience very little deformation relative to the steady case. In both cases, the adhesion sites and nucleus undergo very little deformation.

Mechanosensitive molecule (MSM)

Experimental evidence for MSM (OMKF02)

Studied platelet endothelial cell adhesion molecule 1 (PECAM-1)

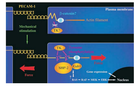


Coated magnetic beads with antibodies against extracellular domain of PECAM-1. Attached beads to ECs and applied magnetic force.

Results

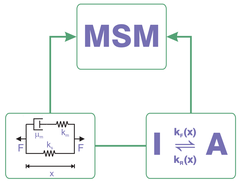
PECAM-1 associated with beads was tyrosine phosphorylated

Solely binding beads or pulling on cell surface using poly-L-coated beads did not phosphorylate PECAM-1



Hypothesis about PECAM-1

Deformation converted into chemical signal by inducing change in chemical state



Hypothesis about MSM

Deforms by applied force

Activates once critical deformation is exceeded

Unimolecular process

Transitions from inactive (I) to active (A) state: I⇌A

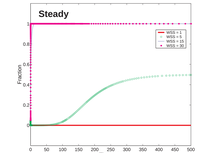
$$\frac{df_A}{dt} = -(k_F + k_R)\,f_A + k_F \qquad f_A(0) = 0.05$$

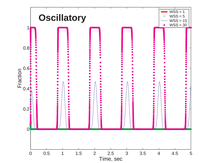
$$k_F(x) = A_F\exp(-a\,x) \qquad k_R(x) = A_R\exp(-b\,x)$$

Activated MSM Fraction

Initial activated fraction is 0.05.

WSS is applied wall shear stress.





Activated MSM fraction: decays to zero for very low WSS under both forcing types; reaches 0.5 under steady but decays to zero under oscillatory for low WSS; reaches 1 under steady but slightly less than 0.5 in amplitude under oscillatory for intermediate WSS; reaches 1 for high WSS under both forcing types. MSM requires intermediate WSS under steady forcing whereas requires high WSS under oscillatory forcing for full activation.

For the future

Combine detection and transmission with transduction

Incorporate adaptation

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